CASE REPORT

How far you can trust c-ANCA?

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SUMMARY

The suspicion of a serious condition arises if a smoker is coughing and losing weight constantly. Serology and imaging are great options for diagnosis, but what is their specificity? A 62-year-old man presented with persistent cough, weight loss and hypoxia. A chest x-ray revealed bilateral interstitial infiltrates. Treatment with several antibiotics failed. Serological results showed antineutrophil cytoplasmic antibodies (c-ANCA) positivity. However, biopsy result indicated cryptogenic organising pneumonia. This case report discloses the differential diagnosis of c-ANCA positive interstitial lung disease in detail.

BACKGROUND

A diagnosis of Wegener's (granulomatosis with polyangiitis) was the first differential diagnosis in this patient owing to cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA) positivity, but pathology result showed cryptogenic organising pneumonia (COP). In this study the importance of biopsy in interstitial lung disease is emphasised. Imaging and serology can lead you to another diagnosis but treatment must be deferred until biopsy result if patient is stable.

CASE PRESENTATION

A previously healthy 62-year-old African-American man presented with a 6-week history of dry cough, shortness of breath and 7-pound weight loss. The patient had dyspnoea with his routine activities and often had prolonged coughing spells. He had a 40-pack-year smoking history. He denied any history of allergies, animal exposure, recent travel or occupational risk factors. There was no personal or family history of pulmonary disease. He was

prescribed a 10-day course of moxifloxacin with no relief in an outpatient clinic. He was treated with piperacillin/tazobactam and levofloxacin for 1 week without improvement in a local hospital. The patient was transferred to our hospital, as his symptoms were progressively worsening without any relief and he had 4-litre oxygen requirement.

The patient was afebrile, tachycardic and tachypnoeic. Respiratory examination revealed coarse, bilateral rhonchi with scattered wheezing. The rest of the physical examinations were unremarkable.

INVESTIGATIONS

Laboratory investigation revealed leucocytosis ($12\,000\text{ WBC/mm}^3$) with eosinophilia (12%) and hypoalbuminaemia (2 g/dl). The rest of the basic laboratory examinations were unremarkable. Blood and sputum cultures did not show any growth. Eosinophilia and the persistence of the symptoms led us to think out of the box. Further laboratory tests were obtained. Erythrocyte sedimentation rate was 101, c-ANCA was positive (1:320).

An initial chest x-ray showed bilateral interstitial shadows (figure 1). A CT revealed bilateral, patchy ground-glass opacities with areas of honeycombing (figures 2 and 3). Pulmonary function test showed mild airflow obstruction with severely reduced diffusion capacity. Bronchoscopy was performed. Bronchoalveolar lavage (BAL) revealed moderate lymphocytic inflammation throughout the tracheo-bronchial tree without significant eosinophilia. Bronchoscopic biopsies were inconclusive hence video-assisted biopsy of lung was obtained.

DIFFERENTIAL DIAGNOSIS

Non-infectious causes should be considered in differential diagnosis of pneumonia if the treatment

Figure 1 Chest x-ray at presentation.

Figure 2 Bilateral patchy ground-glass appearance shown in chest CT.

To cite: Akturk HK, Vashisht P. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-008555

Figure 3 Areas of honeycombing shown in chest CT.

failed with multiple antibiotics and the presence of negative cultures. Most interstitial lung diseases share the same symptoms and similar radiological findings.¹

C-ANCA has been demonstrated in several lung diseases; however, the most common cause is granulomatosis with polyangiitis, formerly known as Wegener's granulomatosis.¹ It is a common practice to label c-ANCA with granulomatosis with polyangiitis. Positive ANCA results must be confirmed with ELISA tests. C-ANCA is an immunofluorescence assay whereas proteinase-3 antibody (anti-PR3) is an antigen-specific ELISA test. Immunofluorescence with ELISA testing confirmation increases the positive predictive value of an ANCA assay.²

In this patient, anti-PR3 was positive but myeloperoxidase antibody (anti-MPO) was negative. This serology confirmed a true positive c-ANCA result. C-ANCA plus anti-PR3 have specificity up to 99% for granulomatosis with polyangiitis.³

Differential diagnoses were granulomatosis with polyangiitis owing to confirmed c-ANCA assay; Churg–Strauss syndrome owing to c-ANCA positivity and eosinophilia and idiopathic acute eosinophilic pneumonia owing to hypoxia and eosinophilia. However, none of these symptoms are non-specific.

Granulomatosis with polyangiitis is an ANCA-associated vasculitis predominantly affecting the lungs. Renal and nasal involvements are also common. Its hallmark features include necrotising granulomatous inflammation with small- and medium-sized vessel vasculitis.

Figure 4 Fibroblastic proliferation shown in biopsy specimen.

Figure 5 Intra-alveolar granulation tissue shown in biopsy specimen.

Churg–Strauss syndrome is an ANCA-associated vasculitis characterised by asthma, chronic rhinosinusitis and peripheral eosinophilia with skin involvement. Histopathological features are eosinophilic infiltration, giant cell vasculitis and necrotising granulomas.

Idiopathic acute eosinophilic pneumonia is characterised with acute onset fever and hypoxia. It is mostly associated with new onset smoking. Analysis of BAL fluid often shows a high number of eosinophils. Lung biopsy shows diffuse alveolar damage with eosinophilic infiltrates.

Video-assisted lung biopsy of this patient showed fibroblastic proliferation and granulation tissue filling terminal bronchioles and alveolar spaces (figures 4 and 5). These changes are consistent with cryptogenic organising pneumonia.

TREATMENT

In this patient, after histopathological diagnosis of cryptogenic organising pneumonia high doses of intravenous steroids were started and followed by oral taper. He quit smoking at discharge. He was discharged with 4 litre of home oxygen.

OUTCOME AND FOLLOW-UP

His pulmonary function tests improved dramatically with the steroid therapy. The functional capacity increased and oxygen dependence decreased at a 4 week follow-up appointment. He will continue oral steroids at least for 6 months and he will be seen in 3-month follow-ups.

DISCUSSION

The diagnosis in interstitial lung disease is challenging. Transbronchial biopsies usually do not provide sufficient samples and an open/video-assisted lung biopsy is recommended to confirm the diagnosis. Histological sampling is imperative because corticosteroids and cytotoxic agents are not indicated in some differential diagnoses.

Cryptogenic organising pneumonia, previously termed as bronchiolitis obliterans-organising pneumonia, is a clinical, radiological and pathological diagnosis, when no definite aetiology such as infection or connective tissue disease is found. The onset of illness is usually acute and presents as a flu-like illness. The non-specific symptoms of malaise, cough, fever and dyspnoea occur in more than two-thirds of the patients.⁴ Men and women are affected equally in most series and are usually aged between 50 and 60 years.⁴ CT results show patchy ground-glass opacities more frequently in the periphery of the lower

lung zone.⁴ The reversed halo sign which is a CT pattern defined as a focal round area of ground-glass attenuation surrounded by a crescent or ring of consolidation is seen in approximately 20% of patients with COP.⁵ Pathological diagnosis is crucial in cryptogenic organising pneumonia. The common negative findings are absence of granulomas, necrosis and vasculitis.

Glucocorticoids are the first-line therapies and recommended for 3–6 months. Relapses are common when glucocorticoids are withdrawn early. Immunosuppressive therapies are usually not needed as this condition responds well to steroids.^{4 6}

Learning points

- It is critical to understand the relevance of immunological tests and the diagnosis should not be made solely on their basis.^{6 7}
- Although cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA) plus proteinase-3 antibody have a specificity of 99% for granulomatosis with polyangiitis; it should be reviewed in the context of the overall picture.^{3 8}
- To avoid false positivity, confirm positive ANCA results with ELISA tests.
- An inappropriate diagnosis based solely on the results of antibody testing could have serious consequences.^{8 9}

Contributors All authors treated the patient, had full access to the data and participated in preparing the abstract.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

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